A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940s

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The Medical Research Council undertook two controlled clinical trials of potentially curative drugs in the United Kingdom in the 1940s. The first trial, carried out in 1943-4 to investigate patulin treatment for the common cold, was arguably the first double blind curative trial with concurrent controls in the general population in modern times.[1] It was also probably one of the last with non-randomised or quasi-randomised[2] allocation of subjects, but it used technology of the highest order then available. The MRC Patulin Clinical Trials Committee (1943) was chaired by Sir Harold Himsworth, and its statisticians were M Greenwood and W J Martin.

The second trial, carried out in 1947-8 to evaluate streptomycin in tuberculosis, is widely accepted as the first randomised curative trial.[3] The MRC Streptomycin in Tuberculosis Trials Committee (1946) was chaired by Sir Geoffrey Marshall, and the statistician was Sir Austin Bradford Hill. As a member of the MRC scientific staff, I was secretary to both committees.

Summary points

- The MRC undertook two controlled drug trials in the 1940s
- In a controlled, double blind mass trial of patulin for the common cold, subjects were allocated alternately to study groups
- In the first streptomycin trial, patients were allocated randomly to groups, but the trial was not double blind or placebo controlled
- Menaces such as HIV infection and multiple drug resistance have dampened the optimism enjoyed by researchers in the middle of this century

Patulin trial

During the second world war, and a few years after the discovery of penicillin, a London biochemist reported that a group from the Royal Navy had shown that a product he had extracted from another penicillium, *Penicillium patulinum*, was beneficial in the common cold. The news spread to other scientists—there was discussion in the *Lancet* on patulin's chemical and biological properties—and it spread to the media. Headlines such as "More valuable than penicillin?" and (more dubiously) "Will it make our service men fight better?" brought patulin to the attention of the public. Pressure mounted, and the MRC appointed their trials committee.

I was asked to assess patulin by means of a controlled mass trial. With the help of Joan Faulkner as coordinator, over a thousand office and factory workers with colds were enrolled from centres nationwide. (Not easy in wartime, when many railway stations carried false names in the fear of German invasion.) Meanwhile some drug companies had agreed with the MRC to dispense the patulin and placebo. The operation started in Cardiff. We decided on an alternation procedure for allocating subjects to study groups.

The doctor and the patient were blinded to the nature of the contents of each treatment bottle and to the code letter for the treatment. Special precautions were taken in addition to using four treatment codes—Q, R, S, and T. A nurse made the allocations in strict rotation in a separate room, filed the record counterfoil there, and detached the code label for the appropriate bottle (which the patient retained throughout the trial) before returning the patient to the doctor. The statisticians passed this as an effectively random concurrent allocation of patulin or control solution to the participants, all of whom had colds. In the event, the trial results analysed showed no protective effect—a disappointing outcome for a rigorously controlled trial and perhaps the last of its kind.

POPPERFOTO

Tuberculosis treatment in the 1940s: Broomfield Hospital, near Chelmsford

The first streptomycin trial

In 1996, BBC's Radio 1 started a weekly programme of short flashbacks recording events of 50 years ago. The producers wanted to celebrate the first use of streptomycin against tuberculosis in the United Kingdom. I saw the script. It was stirring stuff—a woman at death's door … given the drug … life saved. Sadly, I had to object because all the streptomycin imported into the United Kingdom was supposed to have been for the clinical trial a year later. The BBC agreed to a change; the controlled trial had triumphed over anecdotal experience.

In 1944 in the United States, Waksman et al had discovered streptomycin. (Shortly afterwards my wife and I met Waksman and found him an intriguing personality, steeped as much in his music as in his science.)

In 1946, the British government imported a small amount of streptomycin, and it trickled down to the MRC. The council formed a trials committee (see above; survived by Professor Guy Scadding and myself). Then a new MRC Tuberculosis Research Unit was set up to assess the drug by clinical trial (director, myself; deputy and clinical coordinator, Marc Daniels; and statistical adviser, Austin Bradford Hill, director of the MRC Statistical Research Unit).

It might have been expected that the trials committee would discuss Bradford Hill's statistical approach to the forthcoming trial. But in the archives, including my minutes, the only reference I found to this was the agreement that there should be no placebo injection. The committee evidently assumed that Bradford Hill's approach would be sound and discussed at the "front line," which is where he proposed (to Daniels and me) his novel allocation by random sampling numbers. Both of us were familiar with current procedures and readily incorporated his proposal into our protocol for the trial.

I would like to take this opportunity to comment that several accounts of this first streptomycin trial have omitted all mention of the MRC Tuberculosis Research Unit that executed it. Other commentators, however, do credit the three of us with sharing the design for the unit.[4–7]

The trial proceeded from 1947. The small amount of streptomycin available made it ethically permissible for the control subjects to be untreated by the drug—a statistician's dream. The trial had two main results. Firstly, it showed that streptomycin was effective against pulmonary tuberculosis, but there was evidence of some toxicity and acquired drug resistance (not easily obtainable from the American studies). Secondly, the trial heralded the general conversion of clinical scientists to randomisation.

This was not a case of the doctrine of anecdotal experience knocking at the door and randomisation emerging. Bradford Hill had formed his allocation ideas over several years (with randomisation replacing alternation in order to better conceal the allocation schedule), but had only tried them out in disease prevention. He had also been worried that doctors would be unwilling to relinquish the doctrine of anecdotal experience. Now the curative streptomycin trial gave a boost to his views and subsequent teaching, and resulted, after some years, in the present virtually universal use of randomised allocation in clinical trials.

This first streptomycin trial did not obey all the rules. It was not double blind in relation to the doctors or the patients, nor was it placebo controlled; and the hospital environment during treatment was different for patients and controls. In these respects, therefore, it was inferior to the patulin trial.

Epilogue

The MRC Tuberculosis Research Unit did not die after the trial. It continued to flourish and was expanded by my successor, Wallace Fox, who took over in 1965. The unit developed an international reputation for new antituberculosis drug combinations in the United Kingdom and overseas, including the concept of the current DOTS, directly observed treatment short term (with statistical advice from Austin Bradford Hill and later Ian Sutherland, and continued microbiological contributions by D A Mitchison). But this is outside my brief; as are the menaces of HIV infection and multiple drug resistance that have dampened the mid century confidence that we enjoyed.

Competing interests: None declared.

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A phrase which should inform my practice

A positive response from the GP

My father was in hospital, paraplegic from a cord compression by a secondary from prostate cancer. He would never walk again. He had been looked after brilliantly by people who were without exception fine human beings in each hospital he had attended. But to him, hospitals as institutions were places where he could never feel remotely at ease. Indeed, when courting my mother, a physiotherapist, he would never even go inside the hospital where she worked to meet her but preferred to wait in the street.

My mother was desperately keen to nurse him at home if at all possible. At my suggestion, she rang up her general practitioner, to tell her how things were going and ask her advice. Her response? "I am so glad you have telephoned. I have been trying to get in touch with you." Her warmth and enthusiasm meant so much then, and in the last four months of my father's life until he died peacefully at home. They were far from easy months, which were only possible thanks to a huge investment in resources to care for him at home. As always, the role of a really good general practitioner was pivotal.

Care in the community certainly works, but it is not cheap and sometimes cannot be measured in quality adjusted life years (QALYs); the money spent on my father must have been considerable, and the time he was alive short. However, it is impossible to overestimate the importance to both him and his family of him being able to be at home, despite being paraplegic. Shortly before he died he described his circumscribed life, surrounded by his books and papers, as heaven compared with being in hospital in any state.

Resources on their own would not have been enough without the eagerness of the team to make it work. The general practitioner's immediate response had set the tone for the whole of my father's terminal care and encouraged us all throughout. But it set me a challenge, and perhaps others also; how often when someone whom I am supposed to be serving interrupts my work with a problem do I react with gratitude and enthusiasm, and how often do I see them as merely a nuisance?

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